IL-15 Prepares for Its Clinical Debut

It's been nearly two decades since CCR researcher Thomas Waldmann, M.D., *co-discovered interleukin-*15 (IL-15), *a cytokine and potent stimulator of antitumor memory* CD8+ T *cells. Now, in a major step towards the molecule's clinical development,* Waldmann—*Chief of CCR's* Metabolism Branch—*and his CCR colleagues have started the process of testing* IL-15 *in human cancer patients for the first time.*

It took several years and a major collaboration at the NIH between NCI and the National Institute of Allergy and Infectious Diseases (NIAID) to produce clinical-grade IL-15 for human cancer research. "This is a watershed moment," Waldmann said. "IL-15 is one of the most promising new candidates in cancer immunotherapy. For us to have reached this point is hugely gratifying, considering the long scientific odyssey that might never have happened without the cooperation of CCR's Robert Wiltrout, Ph.D., and Clifford Lane, M.D., Deputy Director for Clinical Research and Special Projects at NIAID."

The IL-15 being used by Waldmann was produced by NCI's Biopharmaceutical Development Program (BDP), part of the Division of Cancer Treatment and Diagnosis (DCTD). During a series of NCI-sponsored workshops, investigators put IL-15 at the top of a list of the most compelling new immunotherapies for cancer treatment. The Cancer Immunotherapy Trials Network (CITN), a newly organized multicenter research consortium funded by NCI and headquartered at the Fred Hutchinson Cancer Research Center in Seattle, Wash., has made IL-15 studies a priority. In addition to Waldmann and Lane, other investigators are beginning clinical research with IL-15 including Steven Rosenberg, M.D., Ph.D., Chief of CCR's Surgery Branch, and a number of extramural scientists, including Jeffery Miller, M.D., the Associate Director of Experimental Therapeutics at the Masonic Cancer Center, University of Minnesota.

> "IL-15 holds great promise for exploiting the immune system to treat cancer and infectious diseases"

"IL-15 holds great promise for exploiting the immune system to treat cancer and infectious diseases," said Wiltrout. "The ability to fully understand its possible benefits to patients has been limited by a lack of commitment from the private sector to develop it for clinical use. Thus, the decision by NCI's CCR and DCTD to partner with NIAID has now resulted

(*Photo:* B. Branson)

Robert H. Wiltrout. Ph.D.

(*Photo: R. Baer*)

Thomas A. Waldmann, M.D., and colleagues.

in the production of clinical grade IL-15 and the initiation of novel clinical trials that would otherwise not have been possible."

Potentially Better Than IL-2

Much of the excitement surrounding IL-15 concerns its ability to stimulate natural killer (NK) and CD8+ T cells without inducing capillary leak syndrome. This reaction, typically associated with a related immunotherapy in clinical use today —IL-2—heightens the risk for organ failure in some patients. What's more, unlike IL-2, IL-15 doesn't trigger regulatory T cells (Tregs or suppressor cells) that might otherwise put the brakes on its therapeutic benefits.

Waldmann co-discovered IL-15 in 1994, at about the same time that Kenneth Grabstein, Ph.D., a scientist with Immunex Research and Development Corporation, in Seattle, Wash., was making the same discovery. Working independently, the scientists found that IL-2 shares its T cell receptor with a related molecule—later called IL-15—with which it has some similarities, but also some important differences. Both IL-2 and IL-15 stimulate T cell proliferation, activate NK cells, and induce immunoglobulin synthesis by human B cells. However, unlike IL-15, IL-2 also participates in activation-induced cell death (AICD) of helper CD4+ T cells, is critical in the maintenance of Tregs, and blocks the persistence of memory CD8+ cells. According to Waldmann, this is how IL-2 helps to eliminate lymphocytes that target self-antigens in autoimmune illness. IL-15, on the other hand, inhibits IL-2's role in AICD, has a positive effect on memory CD8+ cells, and, therefore, favors long-term responses against foreign pathogens.

"So we postulated that IL-15 might be useful for cancer treatment," Waldmann said. "And we and others were able to demonstrate this in a number of mouse models, while also showing that IL-15 had relatively low toxicity. This is what convinced NCI to stimulate funding for the production of clinical-grade IL-15 for further research."

The IL-15 subsequently produced by the BDP (in an *E. coli* expression system) under the direction of Stephen Creekmore, M.D., Ph.D., Chief of NCI's Biological Resources Branch, was then tested in a primate model through a collaborative project involving scientists throughout the NIH. Results published in the journal

(*Photo:* B. Branson)

Kevin Conlon, M.D.

Blood, on May 5, 2011, confirmed what Waldmann and other researchers saw in mouse models: Given by bolus infusion, at doses ranging from 10-50 µg/kg/day for 12 days, IL-15 stimulated NK and memory CD8+ cells with minimal toxicity. Buoyed by these findings, Waldmann and co-authors submitted 2,700 pages of supporting data to the Food and Drug Administration (FDA), along with their Investigational New Drug Application to sponsor a clinical trial in humans with metastatic cancer.

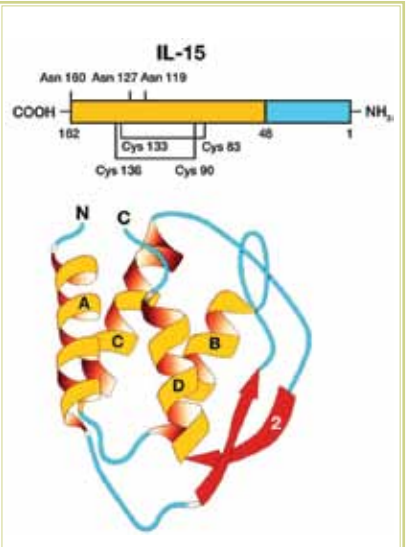
Another Immunotherapy Moves Into the Clinic

With Waldmann as Principal Investigator, a Phase I study of IL-15 is under way. Mirroring dosing protocols from the primate study, the CCR researchers enrolled patients with either metastatic melanoma or metastatic renal cell carcinoma—two illnesses with long-standing, unmet needs for new treatment—and gave them bolus, intravenous infusions of IL-15 at various doses for 12 consecutive days. Unexpectedly, however, human patients proved to be much more sensitive to the cytokine than primates, Waldmann said. "Even at the lowest dose, some patients developed fever and other side effects anywhere from two to four hours after a 30-minute infusion," he said. "So we had to reduce the dose substantially."

According to Kevin Conlon, M.D., a Metabolism Branch clinical collaborator working with Waldmann on the trial, the plan is to complete the bolus infusion study at the lower dose, and then progress to two other exposure scenarios: continuous, low-dose intravenous infusions for ten days, and then subcutaneous injections scheduled Monday through Friday, once a day, for two weeks in a row. Primate data published online November 8, 2011, in the journal *Blood*, suggested that these exposure routes substantially modulate the immune system with fewer side effects.

"We think the problem with bolus infusion has to do with IL-15's pharmacokinetics," Waldmann said. "It has a half-life of 30 minutes, so it drops rapidly to undetectable levels after the peak, which is when we see most of the toxicity. With continuous infusion, we think we'll be able to maintain a more desirable dose level that yields the highest activated lymphocyte count with less fever and hypotension. Subcutaneous dosing might also be appropriate, given that continuous infusion might not be practical, even in this academic, clinical hospital setting."

Howard Streicher, M.D., a Senior Investigator in the NCI's Cancer Therapy Evaluation Program (CTEP), the clinical program in DCTD, is also gearing up for clinical studies with IL-15. He said that CTEP plans to support investigations with the CITN and extramural investigators to focus on finding safe, biologically effective doses over longer time frames, in the order of months. "What we're hoping to do is extend Dr. Waldmann's pioneering work on IL-15 by taking advantage of some new opportunities that are now available in immunotherapy," he said. Indeed, several new approvals have galvanized cancer immunotherapy, Waldmann added, and IL-15 could ride on their success.



(*Image:* T. Waldmann, CCR)

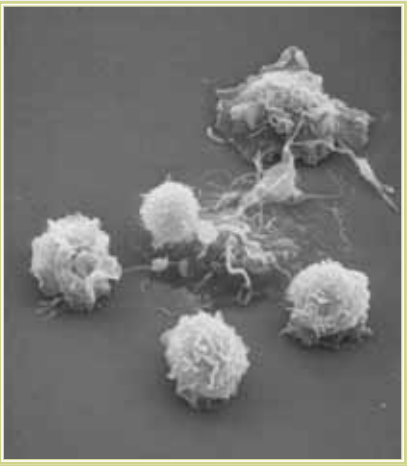
Structure of the IL-15 molecule.

CCR Center of Excellence in Immunology

CCR Director Robert Wiltrout, Ph.D., describes IL-15 as a major theme for NCI's Center of Excellence in Immunology (CEI). One of five centers of excellence in NCI's Intramural Research Program (IRP), the CEI comprises immunology investigators from throughout CCR. Wiltrout chairs the organization, which aims to foster discovery, development, and delivery of novel immunologic approaches for the treatment of cancer and cancer-associated viral diseases.

The CEI's steering committee—made of branch and laboratory chiefs, and key principal investigators—meets once a month to discuss ongoing initiatives and opportunities for further research and hosts a biweekly seminar series to stimulate collaborations. The CEI also provides an interactive forum through which industry representatives can discuss partnership opportunities and material transfer agreements with NCI. Every year, the CEI hosts an annual meeting, with roughly 1,200 to 1,400 registrants, geared towards one of three rotating subject areas: basic immunology, cancer inflammation, and clinical immunotherapy. The most recent meeting, held in Bethesda, Md., on September 22-23, 2011, focused on immunotherapy. In addition, the CEI hosts biannual minisymposia on a range of current subjects such as IL-15's potential in pediatric oncology.

"The CEI provides the infrastructure to develop and support research projects that would be difficult for individuals to accomplish on their own," Wiltrout said. "And it creates opportunities to unite external scientists with our highly skilled and very accomplished, NCI investigators so they may engage in big-picture projects."



(*Image: K. Nagashima, CCR*)

Scanning electron micrograph of immune cells using their projections called microvilli to attach to a target protein.

To learn more about the Center of Excellence in Immunology, please visit its CCR Web site at https://ccrod.cancer.gov/confluence/display/COEI/Home.

> "...the story of IL-15 illustrates the ability of the NIH intramural program to make distinctive and important contributions to biomedical research."

Il-15 and Vaccines in Combination

Streicher's view, shared by others in the field, is that while IL-15 will ideally prove effective as a stand-alone treatment, it might also be useful in combination with other therapies, including monoclonal antibodies or vaccines. "We're not there yet, but it's the kind of thing we envision," he said. "As an NCI program devoted entirely to new therapies, our role is to take a pioneering lead and provide a coordinated development for clinical trials that often would not be done without NCI support. We're just starting to do this with IL-15 now."

Waldmann added that his group has also begun to incorporate IL-15 into vaccines for HIV, anthrax, tuberculosis, human papilloma virus, and other threats. "These are situations in which vaccines alone aren't fully adequate," he said. "There's always a limitation in how long the immune system can be stimulated, and that's where IL-15 provides an advantage: it helps the recall response."

"It's become obvious that this molecule has a lot of potential and that's why it's a central theme in immunology here at CCR. In many ways, the story of IL-15 illustrates the ability of the NIH intramural program to make distinctive and important contributions to biomedical research," Wiltrout said. "Intramural scientists from different institutes worked together to understand the basic biology, colleagues at NCI produced it, and now our NIH clinical center is enrolling the first patients onto clinical trials." The story of IL-15 started a long time ago, but it certainly doesn't end here.

To learn more about Dr. Waldmann's research, please visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?name=waldmann.

To learn more about CCR's clinical trial on IL-15, please visit its Web site at http://bethesdatrials.cancer.gov/clinical-research/search_detail.aspx?ProtocolID=NCI-10-C-0021.